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Problems of Multiple Transfusions

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• The use of blood infusion in large amounts is increasing sharply. Increased knowledge of blood group antigens has alerted physicians to the possible hazards of hemolytic reactions to subgroups that must be eliminated by proper cross-matching techniques. Multiple transfusions of preserved blood often defeat their purpose in control of bleeding, for thrombocytopenia is enhanced. Careful selection of blood or preparations of plasma concentrates offer increased protection to the recipient.

Plastic bag equipment increases the yield of viable platelets and keeps blood in usable condition for longer periods of storage. The use of multiple transfusions has complicated the selection of preserved blood to control pigment metabolism.

DURING THE PAST DECADE there has been a sharp increase in the use of whole blood and plasma components. The vigorous orientation toward rehabilitation of patients with tumors, the greater use of corrective vascular operations and maintenance of comfort in anemic patients have required more transfusions. The expansion of blood requirements in a small teaching hospital are plotted in Chart 1. In 1956, some 4,585,000 units of blood were used in the United States, and even greater needs may be anticipated in the next decade.

The need for multiple transfusions has initiated a remarkable experiment in immunization. The blood group antigens may immunize the recipient as a result of a single transfusion, and future transfusions may become dangerous. Almost 50 blood group factors are known and new factors certainly will be defined. Many of these antigens cause only mild reactions. However, despite the routine accepted laboratory cross-matching procedures for ABO group compatability, over 90 per cent of the transfusions are potentially sensitizing to the recipient.[5] For the most part physicians can protect patients during multiple transfusion therapy if the blood is adequately screened in the laboratory with the techniques available.

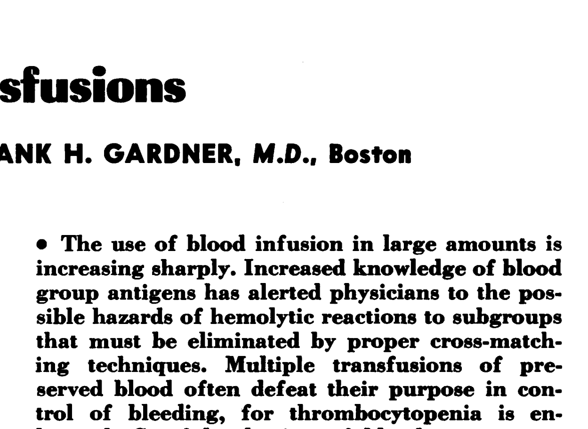

Chart 1.—Use of whole blood in a 260-bed teaching hospital in a period of 13 years (Peter Bent Brigham, 1943-1956). The massive increase in transfusions probably is best related to requirements for vascular operations.

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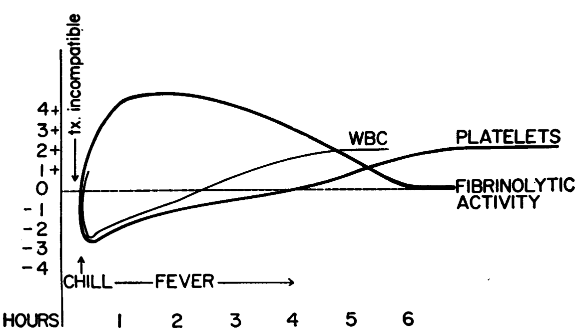

Chart 2.—Reactions in peripheral blood following mismatched transfusion reaction (tx incompatible). The increased plasma fibrinolytic activity is associated with decreased circulating fibrinogen levels. The transient placelet depression will increase bleeding tendency. Modified from Stefanini and Dameshek.[10]

When a patient has massive bleeding, adequate selection and cross-matching procedures may not be feasible. The physiologic response to incompatible blood may enhance the bleeding state. Following the infusion of mismatched blood, the platelet count declines and transient leukopenia occurs (Chart 2). Fibrinolytic activity of the plasma is activated to decrease the circulating fibrinogen level and augment dissolution of recent thrombi necessary for hemostasis.[10] Excessive oozing from tissues may alert the surgeon that a transfusion reaction exists, for anesthesia may mask the chill and fever. The bleeding tendency is increased further by the febrile response and vasodilatation. This reaction persists for several hours and may increase the blood replacement requirements. When possible, an excess of blood should be cross-matched as a safeguard against the hazard of infusing blood without proper safeguards. Patients who have had previous transfusions should be cross-matched with macromolecular substances or evaluated with antihuman globulin rabbit (Coombs) serum to exclude "incomplete" circulating red cell antibodies in the recipient. As a routine policy, in the absence of Rh-negative typing, all recipients who have received five transfusions are cross-matched with Coombs serum for antibodies.

Multiple infusions of stored bank blood collected in National Institute of Health formula A or B, acid citrate dextrose anticoagulant solution will not contain viable platelets. Excessive loss of blood and replacement with bank blood allows the platelets to be "washed out" of the peripheral circulation. Krevans and Jackson[8] correlated platelet counts of the peripheral blood with the number of units of blood infused. As blood replacement exceeds 10 units, thrombocytopenia may be a contributing factor to further bleeding. The circulating platelet levels are not always related to the amount of blood infused, but rather to the time interval in which the blood is administered. Hence, replacement of 15 units in an hour will cause thrombocytopenia, while the same amount of blood given over a period of several days may not affect the platelet count appreciably. As a precautionary policy, the blood bank personnel should alert the physician when 10 units of blood have been administered over a short interval, in order that fresh blood drawn within the hour containing viable platelets may be used. Thrombocytopenia has occurred most frequently, in my experience, during operations on the great vessels and blood replacement in patients with esophageal varices. The bone marrow does not have the capacity to replace or maintain the circulating level of blood platelets rapidly. Craddock and associates[3] demonstrated in dogs the slow recovery of the blood platelet levels after plasmapheresis brought about severe thrombocytopenia. A recovery period of three to five days was necessary for the bone marrow to achieve the pretreatment platelet level. Similar recovery periods have been observed clinically after infusion of 15 to 25 units of banked blood. In essence, a duplication of Craddock's studies may be observed by the infusion of banked blood without viable platelets. The bone marrow does not have a large reservoir of platelets available, as is the case with leukocytes, to restore the circulating platelet levels after depletion by massive bleeding.

Patients with bleeding esophageal varices and portal hypertension need special attention for blood replacement. It many instances moderate thrombocytopenia associated with splenomegaly may have existed before the bleeding episode. These patients appear to have a delayed activation of platelet response to bleeding, a phenomenon that has suggested bone marrow inhibition. Hence, one may not anticipate a rapid recovery of the peripheral platelet values after severe bleeding.[4] Patients with thrombocytopenia undergoing portacaval shunts for portal hypertension should receive platelet concentrates before operation to lessen transfusion requirements and to correct thrombocytopenia. If active bleeding prevents preparation of the patient in this way, the surgeon must recognize that thrombocytopenia may develop more rapidly after the rapid infusion of five to ten units of bank blood. Although such surgical procedures may be begun with preserved blood used at first, fresh whole blood collected in plastic bags should be used after the first few transfusions to assure adequate viable platelets.[6]

The use of bank blood for massive transfusions also carries the risk of thrombocytopenia due to plasma factors. Stefanini[11] demonstrated that stored plasma will depress circulating platelet levels by from 20 to 40 per cent.[11] The platelet depression is

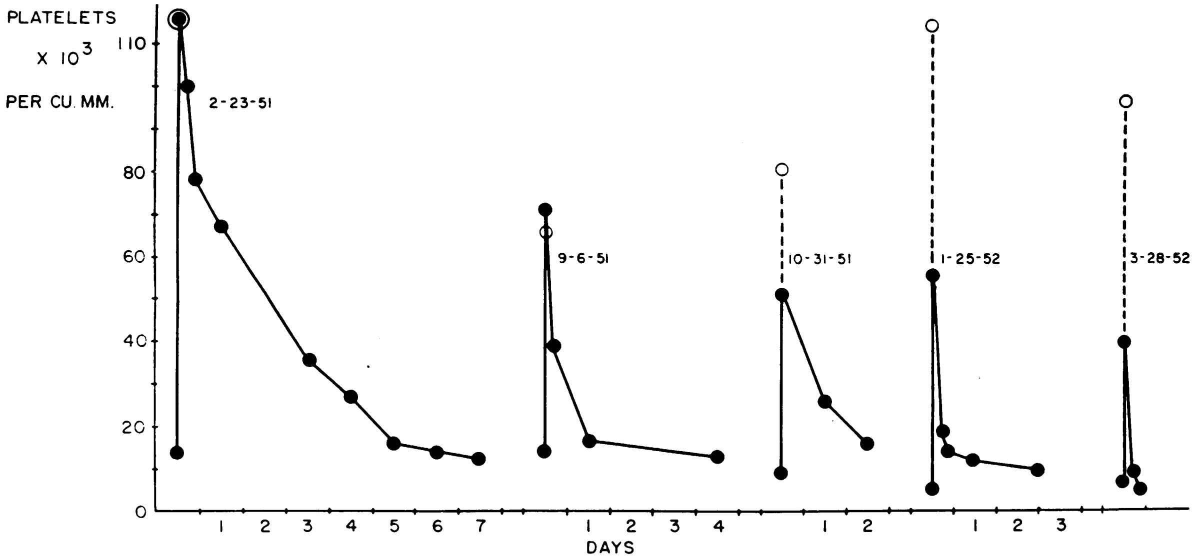

Chart 3.—Evidence of platelet sensitization in patient with aplastic anemia receiving many transfusions. Administration of fresh blood showed initially normal platelet survival of five to seven days. Gradually the survival period decreased and only a temporary appearance of platelets was measured in the patient after transfusion. The dotted lines indicate the theoretical platelet count that was anticipated. The progressive decrease in yield after transfusion suggests immediate platelet destruction as immunization developed.[6]

transient; it exists for a few hours. However, human stored or reconstituted plasma, infused as an adjunct to control hypotension, may well enhance bleeding. This complication may be of clinical importance in a severely burned patient who already has thrombocytopenia related to the injury and needs plasma protein replacement.[9] This transient platelet depression has not been observed when human serum albumin is used, which emphasizes the value of this purified material as a plasma expander.

In Table 1 the viable platelet yield of blood transfused by various procedures is shown. The numerical values for platelets in the in vitro preparation are not important, *per se*, but rather the recovery or yield of circulating (clot promoting) platelets obtained in the recipient should be considered the end point of effectiveness. A sensible program of advanced planning will prevent thrombocytopenia. A patient who has received numerous units of bank blood should have frequent determination of bleeding time. This simple test appears to be the best guide for the sum-total of vascular and plasma factors that influence clotting during multiple transfusions. A nonanemic patient with nonimmune thrombocytopenia should be protected with platelet concentrates. The hemorepellent surfaces offered by plastic bag equipment and tubing has improved the efficiency of preparing platelet suspensions, and good design has helped to insure sterility during the manipulations of centrifugation and concentration. It is important that all recipient infusion sets have protective screen filters removed for the infusion of fresh blood or platelet preparations.

TABLE 1.—*Circulating Yield (Per Cent) of Viable Platelets in the Recipient After Various Transfusion Techniques. (Platelets Are Destroyed by Centrifugation and by Contact with Glass Surface.[6])*

Transfusion Procedure and Equipment	Per Cent of Platelets Viable
Direct, silicone multiple syringe	80 to 90
Fresh (1 hour), plastic bag (ACD/EDTANa_2)	75 to 80
Platelet-rich plasma, plastic bag	60 to 65
Platelet concentrates, plastic bag	50 to 55
Fresh gravity collection, glass vessel	15 to 20
Stored blood, glass vessel (24 hours)	0

Many patients with aplastic anemia, leukemia, nephritis and carcinomatosis have recurring problems of multiple transfusions. Since the procedures in such circumstances are elective, the physician may be assured of compatibility of red cell antigens. However, no satisfactory techniques are available for typing of platelets and leukocytes. The value of blood administered for platelet replacement diminishes and eventually the platelet yield in the recipient is insufficient to protect the patient.[7,12] Transfused platelets may be followed in the recipient for five to seven days. However, if previous transfusions have immunized the patient, the infused platelets may disappear within minutes (Chart 3). The rapid destruction of platelets may be associated with flushing, tachycardia and fever. A similar immune response may be observed following leukocyte sensitization from multiple transfusions. In addition to high fever, severe hypotension and cyanosis may occur, and transient pulmonary infiltrates may be observed in x-ray films.[1] These findings suggest that the leukocytes are agglutinated by white cell antibodies in the recipient from previous transfusions, and that the agglutinated leukocytes are trapped in the pulmonary capillaries.

The severity of these reactions may be altered by centrifuging whole blood and removing the buffy coat before the transfusion. Washing the red cell mass with saline solution will adequately remove leukocytes and platelets from blood to be given to a highly sensitized recipient.[2] In retrospect, probably many febrile reactions classified previously as "plasma protein reaction" in reality were immune responses to leukoagglutinins. If a physician elects to give multiple transfusions, only the red cells should be infused. Removal of the plasma and buffy coat will lessen sensitization of the recipient.

Little interest has been directed toward problems of clinical citric acid intoxication during the transfusion of citrated blood. However, elevated blood citrate levels with intoxication may be seen in patients with liver disease, or during rapid or prolonged transfusions of bank blood. In most normal adults citrate toxicity will not appear until the infusion rate exceeds 5,000 ml. of citrated blood per hour. This rate is now seen frequently with severe bleeding problems (esophageal varices and vascular operations). A patient with impaired liver function or obstruction to the great vessels of the abdomen during vascular operations is liable to have citrate intoxication. Although depression of serum ionized calcium levels and elevated serum citrate levels may be observed, the mechanism for hypotension and altered electrocardiographic patterns may be associated with altered relationships between calcium and potassium ions in the extracellular fluid of the myocardium.[12] Decalcified blood collected from donors by passing across a cation exchange resin should be considered when multiple transfusions are given rapidly.[14] Accessory clotting factors are not altered in decalcified blood, and such transfusions are of real value for patients with severe liver disease. The rapid infusion of calcium-depleted blood will not depress circulating serum calcium levels and interfere with the blood coagulation system. Use of blood with calcium removed for replacement is more ideal than efforts to replace calcium salts parenterally when using citrated blood. If blood decalcified by cation exchange is not available, the hazards of citrate infusion may be controlled in part by more vigorous use of sedimented red cells with plasma expanders to limit the volume of citrated plasma.

Under present regulations most blood banks will retain blood collected in glass bottles with acid citrate dextrose (ACD) anticoagulant solution for 21 days. At the end of three weeks 70 per cent of the preserved red cells are viable after infusion into a recipient. The 30 per cent nonviable red cells are destroyed rapidly during the first 24 hours. If a patient receives only a few transfusions, this does not raise circulating pigment to hazardous levels—namely, about 60 ml. of red cells per unit of blood. If the bank blood has been stored for less than 21 days, the proportion of nonviable red cells will be smaller. If large quantities of blood are required to control bleeding, the physician should recognize that the recipient may have some embarrassment in handling blood pigments derived from the nonviable red cells in preserved blood. Improved viability of red cells may be obtained by collecting blood in plastic bags rather than glass bottles. Utilizing radioactive sodium chromate to evaluate the life span of red cells in recipients, Strumia[13] concluded that blood preserved in plastic bags at 5°C. for 21 days had 87 per cent viability in contrast to 70 per cent in standard glass bottles. Similarly, Walter and co-workers[15] noted 84 per cent survival of blood collected in plastic bags. This method of preservation offers additional protection to decrease the blood pigments that the recipient's reticuloendothelial tissues must handle when a large amount of blood (perhaps the entire blood volume) is replaced with massive transfusions of preserved blood.

The demand on the recipient to clear the plasma of red cell pigments is met in most instances. But the presence of liver disease prevents rapid reduction of plasma bilirubin; and hypotension, along with the associated renal arteriolar vasoconstriction, sensitizes the kidney's reaction to circulating oxyhemoglobin.[17] As an illustrative problem, a 52-year-old man recently underwent operation to correct aortic stenosis. The patient had congestive heart failure before operation but tolerated the procedure well, and the technical results were excellent. His blood was of Group A, Rh negative. Ten units of blood were infused and many of the bottles were close to the accepted expiration date—namely, 18 to 20 days. Because of the storage period, the patient received hemoglobin derived from 275 ml. of nonviable red cells. The stress of the procedure as well as embarrassed liver function resulted in ischemic nephrosis, which undoubtedly was more severe because of the circulating pigment (Chart 4). The patient could not accept or metabolize the destruction of the nonviable red cells and died; the result of a chemical death rather than a complication of operation. Here then is a problem that will need more careful attention in the future. Multiple transfusions should be planned, especially with elective operations, to use relatively fresh bank blood (less than five days old) to protect the patient from a

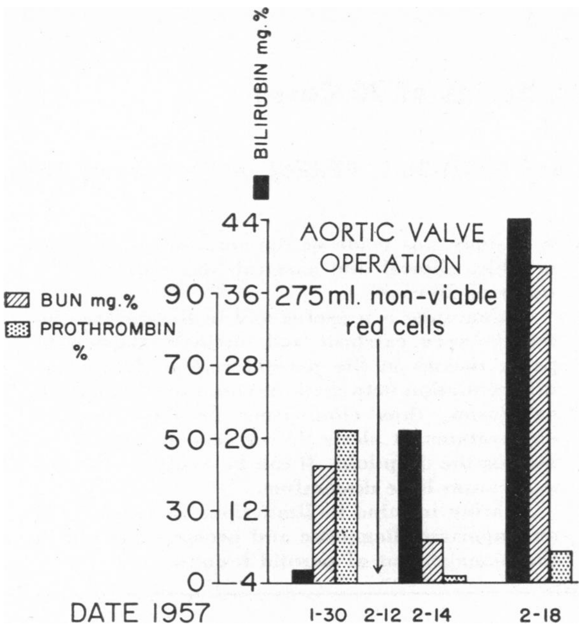

Chart 4.—Development of ischemic nephrosis following infusion of nonviable red cells from old bank blood (18 to 20 days). Progressive pigment retention was indicated by impaired renal excretion (elevated blood urea nitrogen: BUN) and inadequate liver function (depressed prothrombin per cent).

hazardous circulating blood pigment level. The presence of hypotension and poor liver function enhances the complication of acute tubular necrosis by the hemolyzed red cells. This is not a laboratory problem of cross-matching, but rather a "storage lesion" of preserved red cells.

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